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Pathobiology and evolving therapies of coronary artery vasospasm

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ABSTRACT

Coronary artery vasospasm is a known cause of chest pain and requires a high level of clinical suspicion for diagnosis. It also remains in the differential diagnosis for patients presenting with type 2 myocardial infarction. There are few randomized controlled trials for guideline-based prevention and treatment for coronary artery vasospasm. In this article, we review updated concepts in coronary artery vasospasm. Specifically, our aim is to provide current evidence of pathophysiology, identify the risk factors, propose a diagnostic algorithm, review available evidence of evolving therapies, and identify patients who would benefit from automatic implantable cardioverter defibrillators.

KEYWORDS Automatic implantable cardioverter defibrillators; calcium channel blocker; coronary artery vasospasm; nitrates; nitroglycerin; Prinzmetal angina; type 2 myocardial infarction

CME

Target audience: All physicians

Learning objectives: After completing the article, the learner should be able to

1. Discuss the current evidence on the pathophysiology of coronary artery vasospasm
2. Identify the risk factors for coronary artery vasospasm
3. Diagnose and treat coronary artery vasospasm
4. Identify patients who would benefit from an automatic implantable cardioverter defibrillator.

Faculty credentials/disclosure: Dr. Monish A. Sheth is a clinical assistant professor at Baylor Scott and White Medical Center in Temple, a hospitalist with a focus on the cardiac care unit. Dr. Robert Widmer is a clinical assistant professor and interventional cardiologist, experienced in valvular heart disease, cardiac catheterization, minimally invasive cardiac surgery, and health technology/informatics. Dr. Hari Dandapantula is a clinical assistant professor in the Division of Cardiology, specializing in general cardiology, heart failure and transplantation, and cardiac critical care. None of the planners/authors for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Coronary artery vasospasm (CAV) is defined as an "exacerbated, nonspecific contractile response of epicardial coronary artery smooth muscle to various stimuli" or a "reversible, focal and intense coronary vasoconstriction that typically occurs in an epicardial conduit artery segment."[1] Prinzmetal[2] is credited with the first description of chest pain secondary to coronary spasm in 1959. CAV has been shown to manifest in both normal coronary arteries and in coronary arteries with underlying atherosclerotic lesions. In a classic study by Bertrand et al,[3] focal spasms were noted more in patients who complained of angina at rest than in patients with exertional angina, atypical chest pain, valvular heart disease, and cardiomyopathy. CAV was noted in 20% of patients with recent myocardial infarction (MI) compared with 6.2% of patients with a history of MI. Coronary spasm was superimposed on fixed atherosclerotic lesions in 60% of the patients with observed spasm. There are significant ethnic differences in CAV. The incidence of CAV is higher in Korean and Japanese individuals than in Western cohorts.[4] The overall prognosis of CAV was found to be better in a Japanese population with survival as the main endpoint.[5]

CLINICAL PRESENTATION

Chest pain

CAV presents most commonly as chest pain in a young patient at rest between midnight and early morning—potentially related to increased levels of plasma fibrinopeptide A.[6] Classic risk factors of coronary artery disease (CAD) such as hypertension, diabetes mellitus, and hyperlipidemia are not necessarily present in patients with CAV. Usually, attacks of vasospastic angina can be induced by even slight effort in the early morning, but are not induced by even strenuous effort later in the day. Hence, diurnal variation is also observed in exercise tolerance in patients with vasospastic angina.[7]

Myocardial ischemia

On an electrocardiogram (ECG), CAV-induced myocardial ischemia classically presents as ST-segment elevation for variable durations, with resolution of symptoms and ECG changes occurring simultaneously. Approximately one-quarter of CAV cases were associated with type 2 MI in a retrospective analysis involving 171 consecutive patients with definite vasospastic angina based on a serum cardiac troponin I value >99th percentile upper reference limit.[8] In a prospective study of 488 patients with suspected acute coronary syndrome who underwent coronary angiography, every fourth patient had no culprit lesion.[9] These patients underwent intracoronary provocation with acetylcholine (ACh). CAV could be documented in nearly 50% of the patients tested by ACh.[9] Thus, CAV should be considered in the differential diagnosis in patients with type 2 MI and nonobstructive CAD.

Arrhythmia and sudden death

In a multicenter registry study of the Japanese Coronary Spasm Association looking at 1429 patients between 2008 and 2009, 2% had out-of-hospital cardiac arrests and 1% had atrioventricular block.[10] Ventricular arrhythmias are frequent, and they are often related to the severity and duration of ischemia.[11] In the series by Bayes de Luna et al, short episodes of ventricular arrhythmias occurred in 66% of the patients studied by Holter monitoring.[12] Right coronary artery spasm can present clinically as a heart block, while left anterior descending artery spasm has been shown to cause ventricular tachycardia. There are many reported cases of sudden death in patients with CAV that positively correlated with maximal ST elevation on ECG.

FACTORS INFLUENCING CORONARY ARTERY SPASM

Endothelial dysfunction

CAV is associated with a deficiency of nitrous oxide activity with increased endothelin-1 production.[13] There is an abnormal response of the vasospastic artery to ACh in a nitrous oxide–deficient state with a vasoconstrictive response instead of the usual vasodilatory effect. Even though nitrous oxide production is impaired in CAV, it is still present in the spastic artery.[14] There is also evidence of endothelial damage associated with CAV, as evidenced by increased plasma levels of E-selectin and intercellular adhesion molecule-1.[15]

Role of vascular smooth muscle hypersensitivity

Smooth muscle contraction leading to spasm of the artery depends on two factors: the intracellular calcium concentration and smooth muscle sensitivity to calcium. The first step in vascular smooth muscle contractility is phosphorylation of myosin light chain, augmented by Rho-kinase phosphorylation, with a resultant increase in calcium concentration, which is implicated in CAV.[16] In a classic study by Ito et al, the protein kinase C–mediated pathway was shown to be important in the pathogenesis of CAV. The effects of protein kinase C are thought to be mediated through augmentation of calcium influx through the dihydropyridine sensitive L-type calcium channel and also through increased sensitivity of contractile elements to calcium.[17]

Genetic abnormalities

Fujihara et al[18] studied polymorphisms in a Japanese population and in three African subethnic groups and found

three polymorphisms potentially associated with CAV in Japanese patients: paraoxonase 1 (PON1) Q192R (C/G), endothelial nitric oxide synthase (eNOS) E298D (G/T), and eNOS T-786C. Those with African ethnicities shared a high susceptibility to PON1 Q192R (G) like Japanese patients. The e-NOS mutation was seen in Caucasian populations but mostly in Asian populations. Polymorphism in the paraoxonase gene regulates suppression of oxidative stress. Other notable polymorphisms showed by Murase et al[19] studying 2188 Japanese individuals, 500 with CAV and the rest control, found that the NADH/NADPH oxidase p22 phox gene is a susceptibility locus for CAV in men, and the stromelysin-1 and interleukin-6 genes are susceptibility loci in women.

Cigarette smoking

Cigarette smoking is a major risk factor for CAV. The prevalence of cigarette smoking is high in the Japanese population with CAV.[20] There is also evidence of increased circulating products of lipid peroxidation (F2-isoprostanes) in smokers as a cause of oxidative damage,[21] which might be the cause for associated CAV, which indirectly links oxidative stress to CAV. Sugiishi et al demonstrated over a twofold increased risk in smokers for CAV (adjusted odds ratio, 2.41; 95% confidence interval [CI], 1.53–3.82).[22] Yoshimura et al showed the eNOS gene intron 4b/a polymorphism to be involved in smoking-dependent CAD. In their study, multiple logistic regression analysis revealed that the T-786–>C mutation was the most predictive risk factor for CAV, followed by cigarette smoking. Given that those effects are potentially additive, patients carrying the eNOS gene variants should be strongly cautioned against smoking.[23]

Lipid abnormalities

High high-density lipoprotein (HDL) cholesterol/apoA-I levels associated with low apoA-I levels were characteristic in patients with CAV, in whom HDL particles were large, cholesterol-rich, and possibly malfunctioning. Apolipoprotein apo A-I is the main carrier protein of HDL. Miwa et al[24] showed that the serum level of apoA-I in patients with vasospastic angina was significantly lower than in those without vasospasm. Patients with CAV had smaller low-density lipoprotein (LDL) particles, associated not with hypertriglyceridemia but low serum levels of both HDL cholesterol and vitamin E. Small, dense LDL with high susceptibility to oxidation may be linked to the genesis of CAV.[25]

Magnesium deficiency

Magnesium inhibits calcium entry into the cell, causing intracellular calcium deficiency. An increased influx of calcium across the arterial smooth-muscle cell membrane is the postulated mechanism causing CAV.[26] Magnesium deficiency is associated with development of CAV, especially in patients with alcoholism. Alcohol promotes the urinary excretion of magnesium, which in turn is likely to lead to tissue magnesium deficiency.

Role of inflammation

There may be a role of inflammatory mediators in the causation and precipitation of CAV. Kounis syndrome is an allergic angina, which is described as a variant of CAV. The ischemia in allergic reaction is secondary to the release of inflammatory mediators—including histamine, tryptase, chymase, platelet-activating factor, cytokines, and prostaglandins—and leukotriene synthesis, which leads to CAV.[27]

Cardiac catheterization

CAV is shown to occur routinely after coronary angioplasty and can occur at or distal to the catheter site and provoked by the device, by the balloon, and by drug-eluting stent–induced trauma to the endothelium. CAV needs to be ameliorated with intracoronary nitroglycerin to avoid mistakenly stenting a segment of coronary spasm, which could lead to dissection and underdeployment of the stent and subsequent in-stent restenosis.[28]

Substance abuse and medications

Cocaine-associated MI is the most frequent in various research papers. Cocaine's effect on the coronary artery may be mediated through inhibition of noradrenalin reuptake, leading to increased vasomotor tone and hence spasm. El Menyar[29] reviewed 220 articles (>12,000 cases) related to acute MI with normal coronary angiogram. Fifty articles (~100 cases) reported the role of drugs in acute MI secondary to CAV. The diagnosis in most cases was based on the clinical and laboratory findings without provocation. CAV was associated with illicit substances in teenagers, including cocaine, marijuana, alcohol, butane, amphetamine, ecstasy, LSD, heroin, khat (herbal ecstasy), and smoking. Many case reports have shown that ingestion of pseudoephedrine, antimigraine medicine, and dietary supplements containing ephedra is associated with CAV. Cardiac ischemia has been linked to several antineoplastic agents. CAV is a commonly reported effect of cancer therapy that can lead to myocardial ischemia or infarction. The chemotherapy agent 5-fluorouracil or its oral pro-drug capecitabine can result in coronary vascular endothelial dysfunction causing CAV, and possibly coronary thrombosis, with a reported incidence ranging from 1% to 68%.[30]

Others

The renin and angiotensin system (RAS) is known to be closely associated with endothelial function. The action of angiotensin II on smooth muscle cells produces contraction and proliferation. Therefore, increased renin release and angiotensin production from any cause can lead to CAV. CAV as a cause of pregnancy-related MI has been documented. Other triggering factors, such as activation of the

Figure 1. Major factors influencing coronary artery vasospasm.

parasympathetic nervous system and alpha-adrenergic receptors, can lead to CAV; thus, the pathogenesis is multifactorial and complex.[4] The factors influencing coronary artery spasm are summarized in *Figure 1*.

DIAGNOSTIC APPROACH

Electrocardiogram

Attacks of CAV can be associated with transient ST segment elevation, ST segment depression, or negative U wave on an ECG during anginal symptoms, signs that are absent when the patient is asymptomatic. Bayes de Luna et al reviewed ECG changes during occlusive proximal coronary spasm, usually in patients with normal or noncritical coronary stenosis. They found that the most important ECG change during a focal proximal coronary spasm, found in about half the cases, is the appearance of a peaked and symmetrical T wave (subendocardial involvement) that is followed, if the spasm persists, by progressive ST-segment elevation (transmural involvement) that lasts for a few minutes and later progressively resolves. The resolution phase can have a negative T wave. Occasionally, only pseudonormalization of previous negative T waves occurs, sometimes with the appearance of negative U waves. Q waves appear occasionally, especially in cases of preexisting occlusive CAD, but usually do not result in necrosis, as they are transient. Depolarization changes with right bundle branch block are rare, but no evidence of left bundle branch block has been shown secondary to dual blood supply.[11]

Figure 2 shows ECG changes of a patient with CAV-induced chest pain with prolonged 5-fluorouracil infusion, and *Figure 3* shows a coronary angiogram demonstrating minimal nonobstructive CAD.

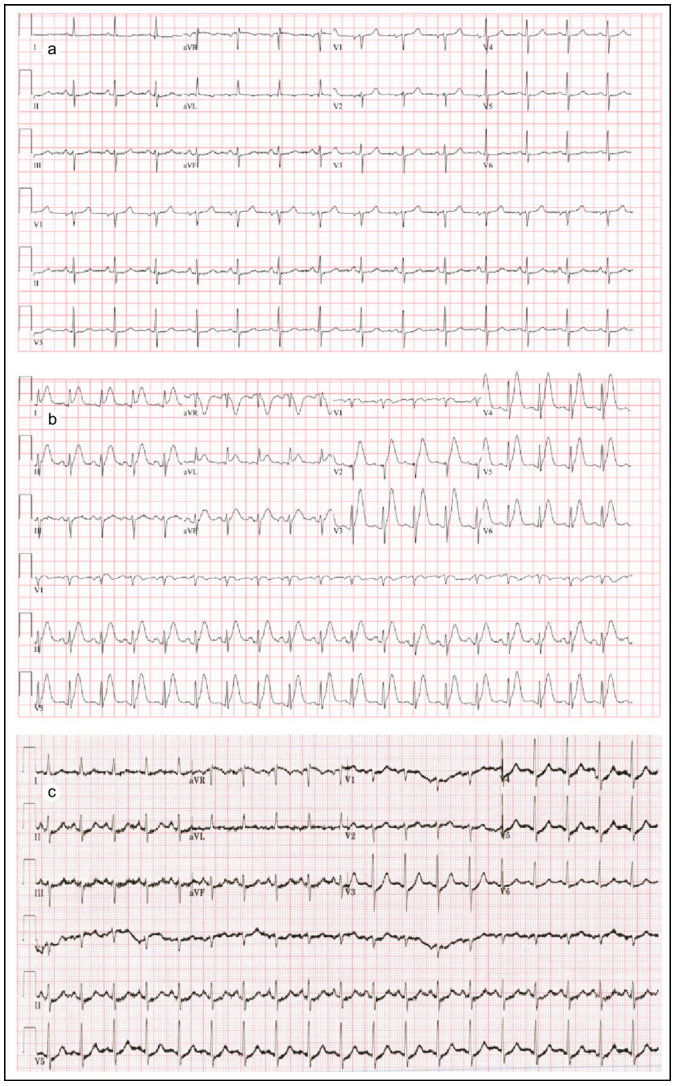

Figure 2. **(a)** Normal sinus rhythm with nonspecific ST changes. **(b)** 5-fluorouracil–induced coronary vasospasm during an angina episode showing ST elevation with hyperacute T wave changes in the anterolateral and inferior leads. **(c)** Resolution of hyperacute T waves and ST elevation. Slight J-point depression only in the inferior and precordial leads after two doses of 0.4 mg sublingual nitroglycerin.

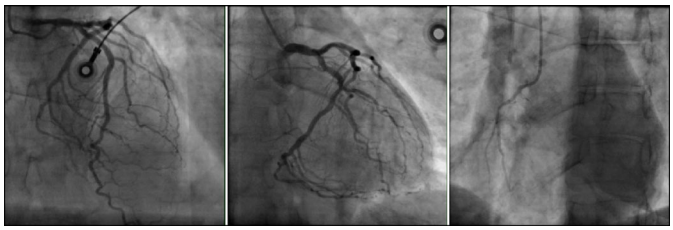

Figure 3. Minimal nonobstructive coronary artery disease.

Holter monitoring

In patients with vasospastic angina, chest pain develops in about 20% to 30% of episodes of ischemic ST change; many events of CAV are asymptomatic. Ventricular arrhythmia may appear during these crises. This may explain the existence of unexpected sudden death due to ischemia.[7] Because attacks are prevalent between night and early

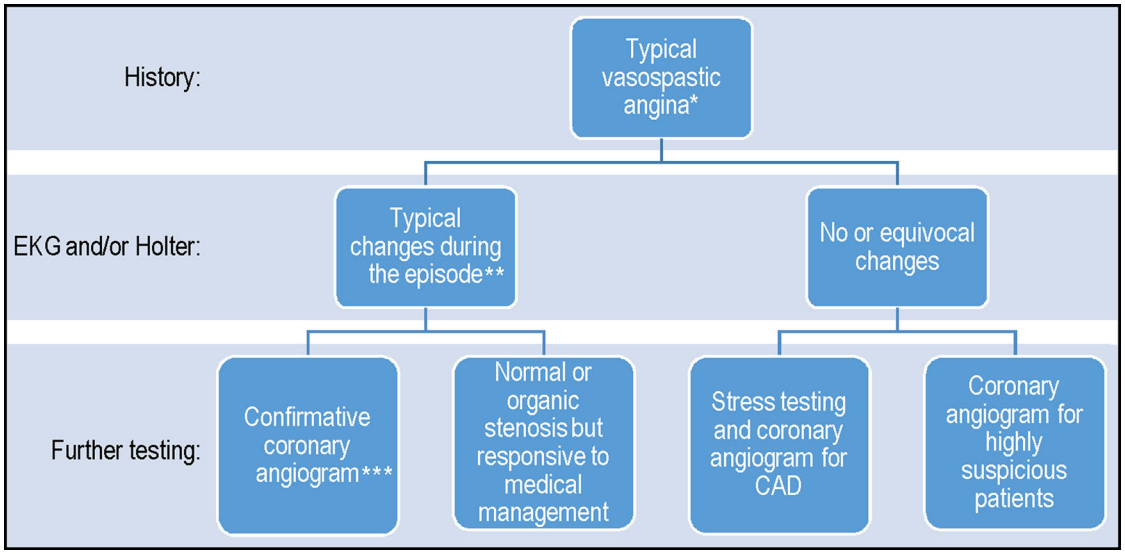

Figure 4. Proposed diagnostic algorithm. *Nitrate-responsive angina is found during a spontaneous episode with one of the following: (1) rest angina, especially between night and early morning; (2) marked diurnal variation in exercise tolerance, reduced in the morning; (3) hyperventilation as a precipitant to an episode; or (4) effect of calcium channel blockers (but not beta-blockers) in suppressing episodes. **Transient ischemic ECG changes or Holter monitoring (during spontaneous episode, including any of the following in at least two contiguous leads): Ischemic change is defined as a transient ST elevation of 0.1 mV or more, an ST depression of 0.1 mV or more, or new appearance of negative U waves, recorded in at least two contiguous leads on the 12-lead ECG. ***Coronary artery spasm: Defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation) According to international standardization of diagnostic criteria for vasospastic angina published in 2017, "definitive vasospastic angina" is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischemic ECG changes during the spontaneous episodes or coronary artery spasm criteria are fulfilled. "Suspected vasospastic angina" is diagnosed if nitrate-responsive angina is evident during spontaneous episodes but transient ischemic ECG changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.

morning at rest, the ischemic ST changes that occur during an attack are often unable to be recorded except in the hospital setting. For patients presenting with recurrent syncope, there might be a role of ambulatory recording of an event. Findings may help determine the need for an automatic implantable cardioverter defibrillator (AICD).

Provocation testing

Demonstration of reversible focal hypercontractility of coronary arteries by various stimuli like hyperventilation or ACh is a mainstay of diagnosing CAV. ACh is widely used in the US. Ergonovine is not available in the USA but is used in Europe. Use of other stimuli like serotonin and histamine has been documented. At present, provocative testing should be employed only by experienced teams. A positive response to provocation testing is defined as transient occlusion (>90% narrowing) of a coronary artery with signs and symptoms of myocardial ischemia (angina/ST changes). Reversal of CAV with intracoronary nitroglycerin is very supportive of the diagnosis.[7] Provocation with ergonovine and ACh has been shown to cause refractory spasm and ventricular arrhythmia in 0.41% to 0.93% of patients exposed to provocation tests. Compared with the complications of diagnostic coronary angiography, selective pharmacological spasm provocation tests have no additional procedure risks, if performed safely with the vessel of interest instrumented with a coronary wire and intracoronary nitroglycerin ready. Performing the spasm provocation tests did not increase the mortality rate in the real world.[31,32]

Other

Myocardial scintigraphy and multidetector-row computed tomography have been studied for diagnosing CAV but are not commonly used. Intravascular ultrasound to look for morphological features and exercise testing to look for diurnal variation in exercise tolerance have been suggested.[7]

Proposed diagnostic algorithm

The algorithm in *Figure 4* shows the process to diagnose CAV and at the same time help identify and/or rule out coexisting obstructive or nonobstructive CAD, which can influence the treatment approach for CAV.[7,33]

THERAPY OF CORONARY ARTERY VASOSPASM

Smoking cessation is beneficial in improving the prognosis for CAV[34] and is considered the single most important factor in treating CAV. Various smoking cessation methods can be tried, such as behavioral therapy, nicotine patches, nicotine gum, oral bupropion therapy, and varenicline therapy.

Avoidance of vasospasm-precipitating medications like beta-blockers,[35] especially nonspecific beta-blockers like propranolol, which cause unopposed alpha action with increased

vascular tone, is recommended in patients with CAV. Beta-blockers have also been shown to precipitate CAV by inhibiting beta-adrenergic–mediated vasodilatation and by increasing vascular permeability to calcium. If beta-blockers are indicated for any reason, they should be combined with calcium channel blockers (CCB).[36] Ergot alkaloids promote CAV and should be avoided. Large-dose aspirin, by inhibiting vasodilator prostacyclin and imbalance with thromboxane A2, promotes CAV; the lowest dose of aspirin should be used if indicated in this patient population. Low-dose aspirin might affect CAV, but studies have shown different results.[37]

Calcium channel blockers are the main line of therapy in patients with CAV. It is recommended to start with a low dose and titrate upwards while watching for the side effects of hypotension, bradycardia, and heart block. Based on their relative affinities for arterial smooth muscle and myocardium, CCBs may be classified into the following groups[38]: dihydropyridines (drug name ends in "pine"), which are relatively selective for arteries; non-dihydropyridines, which include diltiazem (benzothiazepines), which possess equally potent myocardial and arterial effects; and verapamil (phenylalkylamines), which predominantly affect the myocardium. By having both cardiac depressant and vasodilator actions, diltiazem can reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines. Nifedipine is mainly used in acute attacks and recurrent attacks, being a rapid-acting first-generation CCB. Amlodipine, because of its longer half-life and experimental evidence suggesting that it may also bind to non-dihydropyridine binding sites, is used for prophylaxis of CAV.[39]

Nitroglycerin is an endothelium-independent vasoactive agent with the capacity to diminish myocardial oxygen demand by dilating peripheral arteries and veins, thereby causing a resultant fall in left ventricular preload and afterload. It also augments myocardial oxygen supply by dilating epicardial coronary arteries and increasing collateral and subendocardial blood flow.[40] Long-acting nitrates are very useful in patients with circadian-pattern anginal attacks when taken at night. Shorter-acting nitrate therapy is useful for acute CAV. Headache and hypotension are the most common side effects limiting therapy with nitrates. Prospective double-blind studies with CCB compared with nitrates have reported similar efficacy for both agents in reducing spasm occurrence.[41] Some have argued for use of both agents concurrently. CCB and nitrate therapy needs to be balanced with guideline-directed medical therapy in patients with CAD and congestive heart failure.

ACE inhibitors have been postulated historically to treat CAV, and in a recent 5-year clinical follow-up study of 3349 patients diagnosed with CAV, chronic RAS inhibitor therapy was associated with a lower incidence of recurrent angina, total death, and total major adverse cardiovascular events.[42]

Statins[43] are beneficial in treating patients with CAV. There is increasing evidence that 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors improve endothelial dysfunction and reduce cardiovascular events in patients with CAD. A prospective, randomized, open-label study including 64 patients comparing fluvastatin 30 mg/day plus CCB therapy vs conventional CCB therapy alone showed that ACh-induced CAV was significantly reduced in the statin group compared with the nonstatin group (51.6% vs. 21.2%, $P = 0.02$) after 6 months of treatment. Thus, a statin (fluvastatin) may be a novel therapeutic drug for CAV.[44]

Other therapies have also been suggested for CAV. Fasudil, a selective Rho-kinase inhibitor, has been shown to prevent ACh-induced CAV.[45] Denopamine, a beta-1-selective agonist, has been shown to reduce both the frequency and severity of CAV in a small study.[46] Administration of the endothelin antagonist bosentan in a case report resulted in complete resolution of symptoms that were refractory to commonly used antianginals, and these symptoms recurred when the drug was inadvertently withdrawn.[47] Although prospective, randomized, placebo-controlled studies are needed for validation, Sang-yong et al[48] showed that among 21 patients refractory to conventional medications, adding cilostazol for 2 weeks showed a 78.9% relative reduction in the angina intensity score and 73.5% in the angina frequency score ($P < 0.001$). Nicorandil, like nitrates, triggers smooth muscle relaxation via the nitrous oxide pathway and has additional actions as an arterial K + ATP channel agonist, resulting in more "balanced" arterial and venous vasodilatation than nitrates.[49] This agent is not currently available in the US. Amiodarone is another spasmolytic drug that effects smooth muscle relaxation by different mechanisms and appears to be useful for the chronic treatment and prevention of CAV. The vasodilator property of amiodarone is achieved by both direct action and noncompetitive alpha receptor antagonism of coronary vasculature, though it has not been studied much in clinical use.[50] Ketanserin, a serotonin inhibitor, has failed to be of value in the treatment of CAV, as shown in both spontaneous and ergonovine-induced CAV in a small study.[51] Replacement of magnesium has been shown to promote coronary vasodilatation and suppress coronary vasospasm.[52] There is a controversial role of adding vitamin C and vitamin E. Coronary stenting, coronary artery bypass surgery, and surgical sympathectomy have been studied as well.[53,54]

Implantation of an AICD is recommended for patients with recurrent syncope or life-threatening arrhythmias. The study by Ahn et al[55] demonstrated a high rate of recurrent ventricular tachycardia in patients who presented with sudden cardiac arrest (SCA) despite intensive medical therapy (32.4 per 1000 patient-years). They observed a nonsignificant trend limited by small sample size toward lower cardiac mortality in patients who received AICD therapy. Contemporary guidelines support AICD therapy in addition to medical therapy in patients who survive SCA due to

CAV, with a class IIb recommendation.[56] Patients who have survived a cardiac arrest or who have sustained ventricular tachycardia that causes hemodynamic compromise and is not due to a secondary cause (such as acute MI) have a high risk (>40%) of having a recurrent episode of ventricular tachycardia or ventricular fibrillation in the next 2 years, and an AICD for secondary prevention improves survival (31% reduction in mortality in 3 years).[57] Based on a novel risk-stratification system developed by the Japanese CAV Association, a total score from seven predictors—a history of out-of-hospital cardiac arrest, smoking, angina at rest alone, significant organic stenosis, multivessel spasm, ST elevation, and beta-blocker use—can help determine the need for AICD implantation.[58]

In a large retrospective observational study, Ahn et al enrolled CAV patients both with and without SCA across 13 centers in South Korea, examining long-term mortality and ventricular tachycardia recurrence risk. They demonstrated that the incidence of cardiac death (adjusted hazard ratio, 7.26; 95% CI, 4.21–12.50; $P < 0.001$) and all-cause mortality (adjusted hazard ratio, 3.00; 95% CI, 1.92–4.67; $P < 0.001$) was higher in patients with SCA than in those without SCA over a mean follow-up period of 7.5 years. Predictors of SCA included family history of sudden cardiac death, multivessel spasm, and left anterior descending CAV. Interestingly, increased age, hypertension, and hyperlipidemia were associated with a lower SCA risk.[55]

PROGNOSIS

Waters et al identified two features in patients who are symptomatic despite therapy: a lower prevalence of organic coronary stenoses ≥70% and a longer history of rest angina before admission.[59] Spontaneous remission of CAV is a frequent finding in Western populations while persistent symptoms are common in Japanese populations even after therapy for 6 to 12 months, and this is associated with fluctuations in spasm locations. Hence, it is recommended that in Japanese populations, CAV therapy should not be discontinued even after 1 year of therapy even if patients are asymptomatic. Prognosis of patients with CAV is generally dependent on the presence or absence of underlying CAD. Japanese populations have a better prognosis than Western patient populations.[5]

CONCLUSIONS

CAV manifests both in normal coronary arteries and in coronary arteries with underlying atherosclerotic lesions. It is more prevalent in Asian populations than in Western populations. Spontaneous remission is frequent in Western populations, and the overall prognosis is better in Japanese populations given their low prevalence of CAD. A high level of clinical suspicion is required to make and confirm the diagnosis, and there should be a high index of suspicion in type 2 MI. A diagnosis of CAV should not be made without ruling out obstructive epicardial CAD as a cause of angina with transient ECG changes, and treatment should be balanced with guideline-directed medical therapy for coexisting CAD and congestive heart failure. Smoking is the biggest risk modifier, and symptomatic patients should be strongly encouraged to quit. CCBs and nitrates are the cornerstone of therapy. Holter monitoring should be considered for patients presenting with recurrent syncope, and AICDs should be considered for those patients as well as patients who survived cardiac arrest. Further large registries and randomized trials are needed to identify effective individual diagnostic and therapeutic targets.

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Avocations

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